Connecting via Winsock to Dialog

Logging in to Dialog

Trying 31060000009998...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
****
ENTER PASSWORD:
****
Welcome to DIALOG

Dialog level 05.22.00D

Last logoff: 10jul08 09:55:36
Logon file405 11jul08 08:56:07
*** ANNOUNCEMENTS ***
***
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in selected patent and trademark files. Combined with the
comprehensive patent and trademark information on Dialog, file
histories give you the most complete view of a patent or trademark
and its history in one place. When searching in one of the patent
and trademark databases, a link to an online order form is displayed
in your search results, saving you time in obtaining the file
histories you need. See HELP FILEHIST for more information about
how to use the link and a list of files that contain the link.

***The 2008 EMTREE Thesaurus has been added to EMBASE (Files 72, 73,
772, and 972)***

RESUMED UPDATING
***File 120, U.S. Copyrights
***
RELOADS COMPLETED
***File 50, CAB Abstracts
***File 162, Global Health
***
FILES REMOVED
***Files 476/Financial Times & 473/Financial Times Abstracts
***Files 359,959,804, Chemical Economics Handbook
***Files 360,960, Specialty Chemicals Update Program
***
>>>For the latest news about Dialog products, services, content<<<
>>>and events, please visit What's New from Dialog at <<<
>>>http://www.dialog.com/whatsnew/. You can find news about <<<
>>>a specific database by entering HELP NEWS <file number>. <<<
>>>PROFILE is in a suspended state.
>>>Contact Dialog Customer Services to re-activate it.
* * *
SYSTEM HOME
Cost is in DialUnits
Menu System II: D2 version 1.8.0 term=ASCII
*** DIALOG HOMEBASE(SM) Main Menu ***

Information:
1. Announcements (new files, reloads, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training, seminars, etc.)
5. Product Descriptions

Connections:
6. DIALOG(R) Document Delivery
7. Data Star (R)

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/H = Help /L = Logoff /NOMENU = Command Mode

Enter an option number to view information or to connect to an online
service. Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? b 410

11jul08 08:56:07 User217743 Session D736.1
$0.00 0.277 DialUnits FileHomeBase
$0.00 Estimated cost FileHomeBase
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.277 DialUnits

```
File 410:Dialog Comm-of-Interest Newsletters 2008 /Mar
       (c) 2008 Dialog

      Set  Items  Description
      ---  -----  -----------
? set hi ;set hi
HILIGHT set on as ''
HILIGHT set on as ''
? b 155
        11jul08 08:56:12 User217743 Session D736.2
           $0.00     0.115 DialUnits File410
     $0.00  Estimated cost File410
     $0.02  TELNET
     $0.02  Estimated cost this search
     $0.02  Estimated total session cost    0.392 DialUnits

File 155:MEDLINE(R) 1950-2008/Jul 09
       (c) format only 2008 Dialog

      Set  Items  Description
      ---  -----  -----------
? s (tpo or thrombopoietin or mgdf)
          2720  TPO
          2672  THROMBOPOIETIN
           112  MGDF
       S1    4188  (TPO OR THROMBOPOIETIN OR MGDF)
? s s1 and (mutated or mutein or substitute or substituted)
          4188  S1
         32767  MUTATED
           154  MUTEIN
         21422  SUBSTITUTE
         55655  SUBSTITUTED
       S2      52  S1 AND (MUTATED OR MUTEIN OR SUBSTITUTE OR SUBSTITUTED)
? s s2 and (71 or 72 or 76 or 79 or 81 or 82 or 84 or 88 or 90 or 92 or 93 or 182 or 183)
            52  S2
        123596  71
        178468  72
        122591  76
        108923  79
        110582  81
        116585  82
        116191  84
        118110  88
        303625  90
        116694  92
        109279  93
         11451  182
         10119  183
       S3       4  S2 AND (71 OR 72 OR 76 OR 79 OR 81 OR 82 OR 84 OR 88 OR
                   90 OR 92 OR 93 OR 182 OR 183)
? T S3/3,AB/ALL

 3/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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17641337    PMID: 17454774
   Current diagnosis of inherited bone marrow failure syndromes.
   Tamary Hannah; Alter Blanche P
   Department of Pediatric Hematology-Oncology, Schneider Children's Medical
Center of Israel, Petach Tikva, Israel.
   Pediatric hematology and oncology (England)    Mar 2007,  24  (2)  p87-99,
ISSN 1521-0669--Electronic    Journal Code: 8700164
   Publishing Model: Print
   Document type: Journal Article; Review
   Languages: ENGLISH
   Main Citation Owner: NLM
   Record type: MEDLINE; Completed
   Prompt and accurate diagnosis is required for optimal treatment and
genetic counseling of patients with inherited bone marrow failure syndromes
(IBMFS). However, the diverse clinical picture of these syndromes and their
rareness is often associated with diagnostic difficulties. Recently, an
improved diagnostic approach is possible by the cloning of many of the
causative genes. Fanconi anemia (FA) patients belong to at least 12
complementation groups, of which 11 genes have been cloned. An approach
combining an induced chromosomal breakage test, detection of FANCD2-Lby
Western blot analysis, complementation group analysis, and detailed
mutation analysis enables unraveling the causative mutation in the majority
of patients. With the use of such strategies, genotype/phenotype
correlations in FA are evolving. In dyskeratosis congenita mutations in
DCK1, TERC, and TERT genes have been identified, but mutations have been
found in less than half of these patients. In patients with
Shwachman-Diamond syndrome, mutations in the SBDS gene were found in
```

approximately 90% of patients. In Diamond-Blackfan anemia the RSP19 gene is mutated in 20-25% of patients. Heterozygote ELA2 mutations are found in 60-80% of severe congenital neutropenia patients. All patients with congenital amegakaryocytic thrombocytopenia have mutations in the thrombopoietin receptor gene c-Mpl.

3/3, AB/2
DIALOG(R)File 155:MEDLINE(R)
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16360720 PMID: 15858703
Immunophenotype of Down syndrome acute myeloid leukemia and transient myeloproliferative disease differs significantly from other diseases with morphologically identical or similar blasts.
Langebrake C; Creutzig U; Reinhardt D.
University Children's Hospital Muenster, Department of Pediatric Hematology and Oncology, 48129 Muenster. langebra@uni-muenster.de
Klinische Padiatrie (Germany) May-Jun 2005, 217 (3) p126-34, ISSN 0300-8630--Print Journal Code: 0326144
Publishing Model: Print
Document type: Comparative Study; Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND AND OBJECTIVES: Children with Down Syndrome (DS) have a 20-40 fold increased risk of developing acute myeloid leukemia (AML), mainly of the megakaryoblastic subtype (AMKL). Approximately 10% of newborns with DS show transient myeloproliferative disease (TMD) which normally resolves spontaneously. The blast cells of both entities show megakaryoblastic/erythroblastic features (M7/M6) and cannot be distinguished by morphological characteristics. DESIGN AND METHODS: Blast cells of 62 children were analyzed by four-color flow cytometry and dual color fluorescence microscopy. RESULTS: The immunophenotype of blast cells from children with TMD and DS-AMKL is characterized by the expression of CD33 (+)/CD13 (+/-)/CD38 (+)/CD117 (+)/CD34 (+/-)/CD7 (+)/CD56 (+/-)/CD36 (+)/CD71 (+)/CD42b (+)/CD41dim (+)/TPO-R (+)/EPO-R (-)/IL-3-Ralpha (+)/IL-6-Ralpha (-). Non-DS children with morphologically related diseases, i.e. myelodysplastic syndrome (MDS), juvenile myelomonocytic leukemia (JMML), or AML-M6 and AML-M7, did not show this expression profile. CD34 expression was observed in 93% of TMD, but only 50% of DS-AMKL patients. The blast cells of all TMD and DS-AMKL cases were positive for TPO-R and IL-3R, whereas EPO-R and IL-6R were absent. CONCLUSIONS: Immunophenotyping by the use of surface antigens and growth factor receptors is a useful tool to discriminate TMD and DS-AMKL from diseases with morphologically similar or identical blasts. The absence of EPO-R on the blast cells might be a sign of the high expression of the mutated -- and less active -- GATA1 in DS. The higher amount of CD34 co-expression in TMD may be interpreted to indicate that TMD is a slightly more immature disease than DS-AMKL.

3/3, AB/3
DIALOG(R)File 155:MEDLINE(R)
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15891836 PMID: 15279913
Comparative analysis and characterization of mutated thyroid peroxidases with disturbance expressed on the cell surface.
Umeki Kazumi; Kawano Jun-Ichi; Yamamoto Ikuo; Aratake Yatsuki; Kotani Tomio
Laboratory for Clinical Investigation, Miyazaki Medical College Hospital, Kiyotake, Miyazaki 889-1692, Japan.
Molecular and cellular endocrinology (Ireland) Aug 31 2004, 223 (1-2) p77-84, ISSN 0303-7207--Print Journal Code: 7500844
Publishing Model: Print
Document type: Comparative Study; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Five mutated thyroid peroxidases (TPC) with varying degrees of disturbance in cell surface expression, probably owing to misfolding, were comparatively analyzed. CHO-K1 cells transfected with these mutated mRNAs expressed TPO protein in 65.6-82.1% of cells in antibody staining, and the TPCs were located in intracellular structures like the nuclear envelope and ER as well as cytoplasmically like wild-type TPC. When cell surface expression was examined, three mutated TPCs; G533C, D574/L575del--, and G771R-TPCs, were expressed to varying degrees. In contrast, R175Q- and R665W-TPCs were thought not to be expressed on the cell surface, although a vague increment in R175Q-TPO was observed with increasing amounts of mRNA. In the kinetic study, three mutated TPCs having insufficient expression on the cell surface showed delays in decrease at 4 and 8 h after chase, although

between 8 and 24 h after chase they decreased rapidly, as did the two other mutated TPOs. In immunoprecipitation by anti-TPO antibody, G533C-, D574/L575del-, and G771R-TPOs exhibited increasing interaction with calnexin. The combined evidence suggested that some of the mutated TPOs with disturbance in cell surface expression, probably owing to misfolding, exhibited the delay in kinetics of newly synthesized protein as a result of increasing interaction with calnexin and that such TPOs could be expressed to some extent on the cell surface.

3/3,AB/4
DIALOG(R)File 155:MEDLINE(R)
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12420271 PMID: 9354672
Markedly reduced expression of platelet c-mpl receptor in essential thrombocythemia.
Horikawa Y; Matsumura I; Hashimoto K; Shiraga M; Kosugi S; Tadokoro S; Kato T; Miyazaki H; Tomiyama Y; Kurata Y; Matsuzawa Y; Kanakura Y
Department of Internal Medicine II, Osaka University Medical School, Osaka, Japan.
Blood (UNITED STATES) Nov 15 1997, 90 (10) p4031-8, ISSN 0006-4971 --Print Journal Code: 7603509
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Thrombopoietin (TPO) is implicated as a primary regulator of megakaryopoiesis and thrombopoiesis through binding to the cytokine receptor c-Mpl (the product of the c-mpl proto-oncogene). In an effort to determine the pathophysiological role of TPO-c-Mpl system in essential thrombocythemia (ET), we have examined the levels of serum TPO and the expression and function of platelet c-Mpl in 17 patients with ET. In spite of extreme thrombocytosis, serum TPO levels were slightly elevated or within normal range in most, if not all, patients with ET (mean +/- SD, 1.31 +/- 1.64 fmol/mL), as compared with normal subjects (0.76 +/- 0.21 fmol/mL). Flow cytometric and Western blot analyses revealed that the expression of platelet c-Mpl was strikingly reduced in all patients with ET. Furthermore, the expression of platelet c-mpl mRNA was found to be significantly decreased in the ET patients tested. In contrast, almost identical levels of GPIIb/IIIa protein and mRNA were expressed in platelets from ET patients and normal controls. In addition to expression level, activation state of platelet c-Mpl was investigated in ET patients. Immunoblotting with anti-phosphotyrosine antibody showed that no aberrant protein-tyrosine phosphorylation was observed in platelets of ET patients before treatment with TPO, and the levels of TPO-induced protein-tyrosine phosphorylation, including c-Mpl-tyrosyl phosphorylation, roughly paralleled those of c-Mpl expression, suggesting that c-Mpl-mediated signaling pathway was not constitutively activated in platelets of ET patients. These results suggested that the TPO-c-Mpl system may not be directly linked to pathogenesis of ET, and that gene(s) mutated in ET may be important in regulating the levels of c-mpl gene expression in addition to the growth and differentiation of multipotential hematopoietic stem cells.
? s (thrombopoietin or mgdf)
2672 THROMBOPOIETIN
112 MGDF
S4 2696 (THROMBOPOIETIN OR MGDF)
? s s4 and variant
2696 S4
79274 VARIANT
S5 20 S4 AND VARIANT
? ds

Set Items Description
S1 4188 (TPO OR THROMBOPOIETIN OR MGDF)
S2 52 S1 AND (MUTATED OR MUTEIN OR SUBSTITUTE OR SUBSTITUTED)
S3 4 S2 AND (71 OR 72 OR 76 OR 79 OR 81 OR 82 OR 84 OR 88 OR 90 OR 92 OR 93 OR 182 OR 183)
S4 2696 (THROMBOPOIETIN OR MGDF)
S5 20 S4 AND VARIANT
? s s5 not s2
20 S5
52 S2
S6 19 S5 NOT S2
? t s6/kwic/all

6/KWIC/1
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

To study the role of the stress-induced "readthrough" acetylcholinesterase splice variant, AChE-R, in thrombopoiesis, we used transgenic mice overexpressing human AChE-R (TgR). Increased AChE

hydrolytic activity in the peripheral blood of TgR mice was associated with increased **thrombopoietin** levels and platelet counts. Bone marrow (BM) progenitor cells from TgR mice presented an elevated...

...following ex vivo expansion of ARP26-treated CD34+ cells as compared to cells expanded with **thrombopoietin** and stem cell factor. Our findings implicate ACHE-R in thrombopoietic recovery, suggesting new therapeutic...
...; effects--RE; Stem Cell Factor--blood--BL; Thrombopoiesis--drug effects--DE; Thrombopoiesis--radiation effects--RE; **Thrombopoietin**--blood--BL; Transplantation, Heterologous; Whole-Body Irradiation
Chemical Name: Oncorsr1 protein, mouse; Lipopolysaccharides; Neuropeptides; Peptides; Stem Cell Factor; **Thrombopoietin**; Acetylcholinesterase

6/KWC/2
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

...7/GM that differentiates into the erythroid and megakaryocytic lineages by treatment with erythropoietin and **thrombopoietin**, respectively. Upon erythropoietin exposure, overexpressed TEL stimulated hemoglobin synthesis and accumulation of the erythroid differentiation...

...the megakaryocytic maturation-specific glycoprotein IIb and platelet factor 4 transcripts under the treatment with **thrombopoietin**. Consistently, the glycophorin A(-)/glycoprotein IIb(+) fraction increased more slowly in the TEL-overexpressing cells...

...of endogenous TEL proteins in UT-7/GM cells was down-regulated following erythropoietin and **thrombopoietin** exposure. All these data suggest that TEL may decide the fate of human erythrocyte/megakaryocyte...
; Down-Regulation; Erythrocytes--physiology--PH; Erythropoietin--physiology--PH; Humans; Phosphoproteins; Proto-Oncogene Proteins c-ets; **Thrombopoietin**--physiology--PH; Tumor Cells, Cultured
Chemical Name: DNA-Binding Proteins; ETS translocation variant 6 protein; Nuclear Proteins; Phosphoproteins; Proto-Oncogene Proteins c-ets; Repressor Proteins; Erythropoietin; **Thrombopoietin**

6/KWC/3
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

...not yet been identified. During cloning of GH receptor cDNA from salmon, we found a variant with relatively high (38-58%) sequence identity to vertebrate GH receptors and low (28-33...

...in the cytokine receptor type I homodimeric group, which includes receptors for GH, PRL, erythropoietin, **thrombopoietin** granulocyte-colony stimulating factor, and leptin. Transcripts for SLR were found in 11 tissues with...

6/KWC/4
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...binding to 14-3-3xi. The observed phenotypes illustrate an involvement for GP Ibalpha in **thrombopoietin**-mediated events of megakaryocyte proliferation, polyploidization, and the expression of apoptotic markers in maturing megakaryocytes...

...the involvement of a GP Ibalpha/14-3-3xi/PI-3 kinase complex in regulating **thrombopoietin**-mediated responses. An observed increase in **thrombopoietin**-mediated Akt phosphorylation in the truncated variant supported the hypothesis and led to the development of a model in which the GP...

6/KWC/5
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Thrombopoietin and its cognate receptor c-Mpl are the primary regulators of megakaryopoiesis and platelet production...

...a truncated Mpl receptor isoform (Mpl-tr), which results from alternative splicing. The mpl-tr variant is the only alternate mpl isoform conserved between mouse and humans, suggesting a relevant function ...

...retained intracellularly. Our results provide evidence that Mpl-tr exerts a dominant-negative effect on **thrombopoietin**-dependent cell proliferation and survival. We demonstrate that this inhibitory effect is due to down...

...tr, consisting of 30 amino acids of unique sequence, is essential for

the suppression of thrombopoietin-dependent proliferation and Mpl protein down-regulation. Cathepsin inhibitor-1 (CATI-1), an inhibitor of... ...; ME; Polymerase Chain Reaction; Protein Binding; Protein Isoforms; Protein Sorting Signals; Protein Structure, Tertiary; Receptors, Thrombopoietin; Signal Transduction; Thrombopoietin--chemistry --CH; Thrombopoietin--physiology--PH; Transfection ...Chemical Name: Dipeptides; Neoplasm Proteins; Peptides; Protein Isoforms; Protein Sorting Signals; Proto-Oncogene Proteins; Receptors, Cytokine; Receptors, Thrombopoietin; phenylalanyl-glycyl-NHO-Bz; MPL protein, human; Granulocyte-Macrophage Colony-Stimulating Factor; DNA; Thrombopoietin

6/KWC/6
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... lb genes. Moreover, it seems to be present an association with the polymorphisms in the thrombopoietin gene (C4830A and A5713G). Also the role of some genes coding for proteins influencing the...

... metabolism have been closely examined. Many polymorphisms were discovered in the Apo B gene: the variant C-516T was found to be associated with increased LDL levels, whereas the results about...

... LAL sequence, PvuII, MspI, Asp4311Ser) and young AMI are discordant. On the other hand, the variant e4 of the ApoE gene was associated with an increased risk of AMI at young...
...; genetics--GE; Protein C--genetics--GE; Prothrombin--genetics--GE; Risk Factors; Smoking--adverse effects--AE; Thrombopoietin--genetics --GE
...Chemical Name: Platelet Glycoprotein GPIb-IX Complex; Protein C; factor V Leiden; Factor V; Factor VII; Prothrombin; Thrombopoietin; Lipoprotein Lipase

6/KWC/7
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

A functional erythropoietin receptor is necessary for the action of thrombopoietin on erythroid cells lacking c-mpl.
OBJECTIVE: We hypothesized that thrombopoietin (TPO) exerts its mitogenic effects on erythroid cells, at least in part, via an interaction ...

... term growth and proliferation of BaF3/EPO-R cells and to develop a TPO-dependent variant, BaF3/EPO-R(T), which is highly sensitive to and dependent on TPO for its...
... Descriptors; physiology--PH; *Proto-Oncogene Proteins--physiology--PH; *Receptors, Cytokine--physiology--PH; *Receptors, Erythropoietin --physiology--PH; *Thrombopoietin--pharmacology--PD...; effects--DE; Cell Division--drug effects--DE; Cell Line; Mice; Oligodeoxyribonucleotides, Antisense--pharmacology--PD; Receptors, Thrombopoietin
Chemical Name: Neoplasm Proteins; Oligodeoxyribonucleotides, Antisense; Proto-Oncogene Proteins; Receptors, Cytokine; Receptors, Erythropoietin; Receptors, Thrombopoietin; MPL protein, human; Thrombopoietin

6/KWC/8
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... IL-3 or GM-CSF. The EPO defect is not corrected by a constitutively active variant of EPOR. Microarray analysis identified several candidate PU.1 target genes known to affect cytokine...
...; Receptors, Erythropoietin; Recombinant Fusion Proteins--metabolism --ME; STAT5 Transcription Factor; Stem Cell Factor--metabolism-ME; Thrombopoietin--metabolism-ME; Trans-Activators--genetics--GE
...Chemical Name: Activators; proto-oncogene protein Spi-1; Erythropoietin; Green Fluorescent Proteins; Granulocyte-Macrophage Colony-Stimulating Factor; Thrombopoietin; Protein Tyrosine Phosphatase, Non-Receptor Type 6; Protein Tyrosine Phosphatases; Ptpn6 protein, mouse

6/KWC/9
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

...within intron 5 affects the pattern of alternative splicing occurring within exon 6 of the thrombopoietin gene.
OBJECTIVE: A common variant in intron 5 of the thrombopoietin (TPO) gene (4830C>A) has been associated with risk of myocardial infarction (MI). To explore...

...resulted in a small but statistically significant increase in production of the TPO-3 splice variant relative to the full-length transcript

(10.6%+/-0.6%) compared to the 4830C allele...
Descriptors: *Alternative Splicing; *Introns--genetics--GE; *Polymorphism, Single Nucleotide--genetics--GE; *Thrombopoietin--genetics--GE
Chemical Name: Thrombopoietin

6/KWC/10
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

MplK, a natural variant of the thrombopoietin receptor with a truncated cytoplasmic domain, binds thrombopoietin but does not interfere with thrombopoietin-mediated cell growth.
OBJECTIVE: Interaction of thrombopoietin (TPO) with its receptor c-Mpl is responsible for the formation of megakaryocytes and platelets...
Descriptors: *Neoplasm Proteins; *Proto-Oncogene Proteins--metabolism-ME; *Receptors, Cytokine; *Thrombopoietin--metabolism-ME...; Protein Binding; Protein Conformation; Proto-Oncogene Proteins--chemistry--CH; Proto-Oncogene Proteins--genetics--GE; Receptors, Thrombopoietin; Signal Transduction--drug effects--DE; Thrombopoietin--pharmacology--PD
Chemical Name: Neoplasm Proteins; Proto-Oncogene Proteins; Receptors, Cytokine; Receptors, Thrombopoietin; MPL protein, human; Thrombopoietin

6/KWC/11
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

We report a patient with cyclic thrombocytopenia and antiplatelet antibodies, a variant of chronic immune thrombocytopenic purpura (ITP), with a several year history of periodic fluctuation of...
...Descriptors: Recombinant Proteins--administration and dosage--AD; *Recombinant Proteins--therapeutic use--TU; *Idiopathic--drug therapy--DT; *Thrombopoietin--administration and dosage--AD; *Thrombopoietin--therapeutic use--TU...; Thrombocytopenic, Idiopathic--etiology--ET; Purpura, Thrombocytopenic, Idiopathic--immunology--IM; Thrombocytopenia--etiology--ET; Thrombocytopenia--immunology--IM; Thrombopoietin--blood--BL; Thrombopoietin--deficiency--DF
...Chemical Name: IX Complex; Polyethylene Glycols; Recombinant Proteins; polyethylene glycol-recombinant human megakaryocyte growth and development factor; Thrombopoietin

6/KWC/12
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

... i.e., isoforms of the Trp family of proteins. Primary stem cells were cultured with thrombopoietin to allow differentiation into megakaryocytes. The undifferentiated stem cells (CD34(+)) showed mRNA expression of only a spliced variant Trp1A. Immature (CD61(+)/CD42b(low)) and mature (CD61(+)/CD42b(high)) megakaryocytes as well as platelets...
...; Isoforms; RNA, Messenger--metabolism-ME; Sequence Analysis, DNA; Stem Cells--metabolism-ME; TRPC Cation Channels; Thrombopoietin--metabolism-ME
...Chemical Name: Messenger; TRPC Cation Channels; TRPC4 ion channel; transient receptor potential channel-related protein 1; Calcium; Thrombopoietin

6/KWC/13
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Glycoprotein 130 and c-kit signals synergistically induce thrombopoietin production by hematopoietic cells.
... produced by erythroid progenitors stimulates erythropoiesis via gp130 and c-kit signals. Here we examined thrombopoietin (TPO) production by hematopoietic cells cultured with IL-6, sIL-6R, and SCF. Reverse transcription...

...cells generated from cord blood CD34+ cells with the 3 factors expressed a minor splice variant of TPO messenger RNA, P1 delta E2, which can be translated to TPO protein more...
...Descriptors: Membrane Glycoproteins--pharmacology--PD; *Neoplasm Proteins; *Proto-Oncogene Proteins c-kit--pharmacology--PD; *Receptors, Cytokine; *Thrombopoietin--biosynthesis--BI...; Proteins c-kit--physiology--PH; RNA, Messenger--drug effects--DE; RNA, Messenger--metabolism-ME; Receptors, Thrombopoietin; Signal Transduction--drug effects--DE; Thrombopoietin--drug effects--DE; Thrombopoietin--genetics--GE
...Chemical Name: ILEST protein, human; Membrane Glycoproteins; Neoplasm Proteins; Proto-Oncogene Proteins; RNA, Messenger; Receptors, Cytokine; Receptors, Thrombopoietin; Cytokine Receptor gp130; MPL protein,

human; Thrombopoietin; Proto-Oncogene Proteins c-kit

6/KWC/14
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Cloning and functional characterization of a novel c-mpl variant expressed in human CD34 cells and platelets.
The thrombopoietin receptor, c-mpl, is a crucial element not only in thrombopoietin (TPO)-initiated signaling pathways but also in the regulation of the circulating amount of TPO...

... 125)I-rHuTPO. Taken together, these results demonstrate that c-mpl-del, a naturally occurring variant of c-mpl, fails to be incorporated into the cell membrane but might serve as...
... Descriptors: Neoplasm Proteins; *Proto-Oncogene Proteins--physiology--PH; *Receptors, Cytokine--physiology--PH; *Receptors, Immunologic--physiology--PH; *Thrombopoietin--metabolism-ME...; genetics--GE; Receptors, Cytokine--biosynthesis--BI; Receptors, Cytokine--genetics--GE; Receptors, Immunologic--genetics--GE; Receptors, Thrombopoietin; Transfection
Chemical Name: Antigens, CD34; Neoplasm Proteins; Proto-Oncogene Proteins
Receptors, Cytokine; Receptors, Immunologic; Receptors, Thrombopoietin; MPL protein, human; Thrombopoietin

6/KWC/15
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

... to 70,000 Da were easily separated using reversed-phaseHPLC (rpHPLC) or affinity chromatography. A variant of rhIGF-I, where the racemization of a serine residue was detected in the intact...

... glycoprotein. The presence or absence of O-linked sugars on Thr -37 of recombinant human thrombopoietin was rapidly demonstrated by rpHPLC. While the separation of these types of variants is essential...

... that allow the administration of these proteins into humans. Once a correlation exists between the variant and its biological activity, control of the manufacturing process can be better achieved with analytical ...
... ; IP; Mice; Molecular Sequence Data; Protein Folding; Recombinant Proteins--chemistry--CH; Recombinant Proteins--genetics--GE; Thrombopoietin--genetics--GE; Thrombopoietin--isolation and purification--IP; Variation (Genetics)
Chemical Name: Recombinant Proteins; Insulin-Like Growth Factor I; Thrombopoietin; Deoxyribonuclease I

6/KWC/16
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Human thrombopoietin (hTPO) variant cDNAs truncated in the C-terminal regions of wild-type hTPO (332 amino acids) were...

... PCR and expressed in Trichoplusia ni (Tn5) insect cells using a baculovirus expression system. Each variant, hTPO(163 (amino acids 1-163), hTPO(198 (1-198) and hTPO(245 (1-245), was produced in...
Descriptors: *Baculoviridae--metabolism-ME; *Thrombopoietin--physiology--PH...; analysis--AN; Gene Expression; Glycosylation; Humans; Insects--genetics--GE; Insects--metabolism-ME; Polymerase Chain Reaction; Thrombopoietin--genetics--GE; Thrombopoietin--secretion--SE; Transfection
Chemical Name: DNA, Complementary; Thrombopoietin

6/KWC/17
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Thrombopoietin production is inhibited by a translational mechanism
Thrombopoietin (TPO) is a lineage-dominant hematopoietic cytokine that regulates megakaryopoiesis and platelet production. The major...

... which account for 98% of TPO mRNA, were almost completely inhibited, whereas a rare splice variant that lacks exon 2 can be more efficiently translated. Thus, inhibition of translation of the...
Descriptors: *Protein Biosynthesis; *RNA, Messenger--biosynthesis--BI; *Thrombopoietin--biosynthesis--BI...; Sequence; Animals; Base Sequence; COS Cells; Molecular Sequence Data; RNA, Messenger--genetics--GE; Sequence Analysis; Thrombopoietin--genetics--GE
Chemical Name: RNA, Messenger; Thrombopoietin

6/KWC/18
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Megakaryocytopoietic activity of a truncated variant of mouse thrombopoietin.
Thrombopoietin (TPO) is a hemopoietic cytokine that specifically stimulates the growth and development of megakaryocytes. In...
Descriptors: *Hematopoiesis--drug effects--DE; *Megakaryocytes--cytology --CY; *Thrombopoietin--chemistry--CH; Animals; Bone Marrow Cells; Cell Line; Cricetinae; Kringles; Mice; Recombinant Fusion Proteins; Structure-Activity Relationship; Thrombopoietin--pharmacology--PD; Tissue Plasminogen Activator--chemistry--CH
Chemical Name: Recombinant Fusion Proteins; Thrombopoietin; Tissue Plasminogen Activator

6/KWC/19
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Constitutive activation of a variant of the env-mpl oncogene product by disulfide-linked homodimerization.
... mpl is a truncated form of the c-mpl gene which encodes the receptor for thrombopoietin. We investigated the contribution of the Env-Mpl extracellular domain in the constitutive activation of...
... env sequences in the env-mpl fusion gene was not required for oncogenicity. A pathogenic variant, DEL3MPLV, was generated, which differs from MPLV by the deletions of 22 amino acids of...
...; Inbred DBA; Molecular Sequence Data; Proto-Oncogene Proteins --chemistry--CH; Receptors, Immunologic--chemistry--CH; Receptors, Thrombopoietin; Recombinant Fusion Proteins--chemistry--CH; Recombinant Fusion Proteins--genetics--GE; Sequence Deletion; Variation (Genetics); Virulence...
...Chemical Name: Viral; Disulfides; Gene Products, env; Neoplasm Proteins; Proto-Oncogene Proteins; Receptors, Cytokine; Receptors, Immunologic; Receptors, Thrombopoietin; Recombinant Fusion Proteins; MPL protein, human
? t s6/3,ab/6,9,13

6/3,AB/6
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

15895246 PMID: 15284679
Genetic risk factors in myocardial infarction at young age.
Incalcaterra E; Hoffmann E; Averna M R; Caimi G
Cardiology Section, University of Palermo, Palermo, Italy.
Minerva cardioangiologica (Italy) Aug 2004, 52 (4) p287-312, ISSN 0026-4725--Print Journal Code: 0400725
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
The role of genetic susceptibility to coronary artery disease (CAD) seems to be quite important in young patients. In the last years the attention has been focused on polymorphisms influencing some biological functions (coagulation and fibrinolysis, platelets, vascular function, lipid metabolism, inflammation). The study of prothrombotic polymorphisms has kindled a deep interest. The role of atherosclerosis and thrombosis is different in the different ages. In all the studies we examined, the polymorphism G20210A in the prothrombin gene was associated with an increased risk of acute myocardial infarction (AMI) in young people, especially when other risk factors were present. Contradictory results have been found in the studies on Factor V Leiden: according to many authors the activated protein C resistance (APCR) is associated with an increased risk of AMI only in smokers, above all if women. On the other hand, some polymorphisms of the Factor VII gene seem to be protective. Young AMI could be also caused by a reduction of the fibrinolytic activity, as it was found when the allele 4G in the promoter of plasminogen activator inhibitor (PAI) gene is present. The attention has also been focused on the effects of variations in genes that influence platelet functions. According to a metanalysis of studies published up to 1999, there is no association between the polymorphism PlA1/A2 of the GP IIIa gene and young AMI, whereas there is doubt about the role of the polymorphism in the GP IIb e GP Ib genes. Moreover, it seems to be present an association with the polymorphisms in the thrombopoietin gene (C4830A and A5713G). Also the role of some genes coding for proteins influencing the vascular functions has been valued. Few studies were performed on genetics of the renin-angiotensin-aldosterone system and the results are insufficient and contradictory, such as those about the association between the polymorphism G894T in the eNOS gene or the polymorphism C677T in the MTHFR gene and young AMI. Genes coding for proteins involved in the lipid metabolism have been closely examined. Many polymorphisms were discovered in the Apo B

gene: the variant C-516T was found to be associated with increased LDL levels, whereas the results about the association between this and other polymorphisms in the same gene (I/D of LAL sequence, PvuII, MspI, Asp4311Ser) and young AMI are discordant. On the other hand, the variant e4 of the ApoE gene was associated with an increased risk of AMI at young age in many works. In the last years, a particular interest has kindled the study of the relationship between inflammation, atherosclerosis and CAD. Even if the studies performed are few, it was found an association between young AMI and polymorphism C-260T in the CD14 gene, between coronarics atherosclerosis and polymorphism A516C in the E Selectin gene or polymorphisms Leu125Val and Ser563Asn in the PECAM1 gene.

6/3,AB/9
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

15250241 PMID: 12829024
The -4830C>A polymorphism within intron 5 affects the pattern of alternative splicing occurring within exon 6 of the **thrombopoietin** gene.
Webb Karen E; Martin John F; Cotton James; Erusalimsky Jorge D; Humphries Steve E
Centres for Cardiovascular Genetics, British Heart Foundation Laboratories, Royal Free and University College Medical School, Rayne Building, 5 University Street, London WC1E 6JF, England.
Experimental hematology (Netherlands) Jun 2003, 31 (6) p488-94, ISSN 0301-472X--Print Journal Code: 0402313
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: A common variant in intron 5 of the **thrombopoietin** (TPO) gene (-4830C>A) has been associated with risk of myocardial infarction (MI). To explore the molecular mechanism of this association, the ability of the intron to act as a transcription enhancer and to influence mRNA splicing was tested. METHOD AND RESULTS: In HepG2 cells the presence of intron 5 upstream of the TPO promoter decreased promoter activity to between 60% and 30%. This effect was orientation dependent; in the reverse orientation, intron 5 caused a twofold greater decrease in promoter activity compared to the forward orientation. However, the effects were similar with either the C or the 4830A allele. An in vitro exon trapping system was used to study the effect of the polymorphism on splicing events in exon 6. The full-length (TPO-1) and three previously reported splice variants (TPO-2, TPO-3, and TPO-5) were identified. The 4830A allele resulted in a small but statistically significant increase in production of the TPO-3 splice variant relative to the full-length transcript (10.6%+/-0.6%) compared to the 4830C allele (8.3%+/-0.6%) (p=0.02). Generation of TPO-5 was also slightly increased, but this did not reach significance. CONCLUSION: The identification of a potential "silencer" sequence in intron 5 of the TPO gene demonstrates the complexity of control of expression of the gene. Although the precise role of the different splice variants is not known, the finding that the 4830C>A sequence change alters their relative amounts, suggests a possible molecular mechanism whereby TPO genotype may influence the risk of MI.

6/3,AB/13
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

13874859 PMID: 11197211
Glycoprotein 130 and c-kit signals synergistically induce **thrombopoietin** production by hematopoietic cells.
Matsui A; Sato T; Maekawa T; Asano S; Nakahata T; Tsuji K
Department of Clinical Oncology, University of Tokyo, Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan.
International journal of hematology (Ireland) Dec 2000, 72 (4) p455-62, ISSN 0925-5710--Print Journal Code: 9111627
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have reported that simultaneous activation of glycoprotein (gp) 130 and c-kit signals by interleukin (IL)-6, soluble IL-6 receptor (sIL-6R), and stem cell factor (SCF) promotes proliferation of human hematopoietic progenitor cells and their differentiation into erythroid, myelocytic, and megakaryocytic cells. We recently found that erythropoietin produced by erythroid progenitors stimulates erythropoiesis via gp130 and c-kit signals. Here we examined **thrombopoietin** (TPO) production by hematopoietic cells cultured with IL-6, sIL-6R, and SCF. Reverse transcription-polymerase chain reaction analysis indicated that

hematopoietic cells generated from cord blood CD34+ cells with the 3 factors expressed a minor splice variant of TPO messenger RNA, P1 delta E2, which can be translated to TPO protein more efficiently than regularly spliced isoforms. The reduction in c-mpl, receptors for TPO, by antisense oligodeoxynucleotides suppressed the generation of erythroid, myelocytic, and pluripotent progenitors in suspension culture, plus colony formation of megakaryocytic progenitors in addition to these progenitors in clonal culture of cord blood CD34+ cells with IL-6, sIL-6R, and SCF. The addition of anti-human TPO antibody to the clonal culture also suppressed colony formation. These findings indicate that TPO production by hematopoietic cells stimulated by IL-6, sIL-6R, and SCF is involved in promoting their own growth.

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? logoff

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        11jul08 09:02:31 User217743 Session D736.3
             $4.94     1.404 DialUnits File155
                $0.95   19 Type(s) in Format 95 (KWIC)
                $1.68   7 Type(s) in Format  4 (UDF)
             $2.63   26 Types
      $7.57  Estimated cost File155
      $1.86  TELNET
      $9.43  Estimated cost this search
      $9.45  Estimated total session cost    1.796 DialUnits
Logoff: level 05.22.00 D  09:02:31
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Connecting via Winsock to Dialog

Logging in to Dialog

Trying 31060000009998...Open

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DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
ENTER PASSWORD:
 ********
Welcome to DIALOG

Dialog level 05.22.00D

Last logoff:  11jul08 09:02:31
Logon file405 11jul08 09:09:13
>>>PROFILE is in a suspended state.
>>>Contact Dialog Customer Services to re-activate it.
* * *
SYSTEM HOME
Cost is in DialUnits
Menu System II:  D2 version 1.8.0 term=ASCII
                      *** DIALOG HOMEBASE(SM) Main Menu ***

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Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? b 410

        11jul08 09:09:14 User217743 Session D737.1
             $0.00     0.321 DialUnits FileHomeBase
      $0.00  Estimated cost FileHomeBase
      $0.00  Estimated cost this search
      $0.00  Estimated total session cost    0.321 DialUnits

File 410:Dialog Comm-of-Interest Newsletters 2008 /Mar
        (c) 2008 Dialog

       Set  Items  Description
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10/614481 09/07/2006

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? set hi ;set hi
HILIGHT set on as ''
HILIGHT set on as ''
? B 155
        11jul08 09:09:25 User217743 Session D737.2
              $0.00     0.115 DialUnits File410
      $0.00   Estimated cost File410
      $0.05   TELNET
      $0.05   Estimated cost this search
      $0.05   Estimated total session cost    0.436 DialUnits

File 155:MEDLINE(R) 1950-2008/Jul 09
        (c) format only 2008 Dialog

      Set   Items   Description
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? S THROMBOPOIETIN OR MGDF
            2672   THROMBOPOIETIN
             112   MGDF
      S1    2696   THROMBOPOIETIN OR MGDF
?  s s1 and (structure or structural) and analysis
            2696   S1
          677650   STRUCTURE
          282511   STRUCTURAL
         3123455   ANALYSIS
      S2      32   S1 AND (STRUCTURE OR STRUCTURAL) AND ANALYSIS
? t s2/ti/all

 2/TI/1
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

  Mouse growth and differentiation factor-5 protein and DNA therapy
potentiates intervertebral disc cell aggregation and chondrogenic gene
expression.


 2/TI/2
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

   Molecular features crucial to the activity of pyrimidine benzamide-based
thrombopoietin receptor agonists.


 2/TI/3
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

  A rational chemical intervention strategy to circumvent bioactivation
liabilities associated with a nonpeptidyl thrombopoietin receptor
agonist containing a 2-amino-4-arylthiazole motif.


 2/TI/4
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

  [Formation of platelets from cord blood CD34+ cells-derived
megakaryocytes induced by S-nitrosoglutathione]


 2/TI/5
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

   Structural modeling and analysis of signaling pathways based
on Petri nets.


 2/TI/6
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

  Establishment of cell lines that exhibit correct ontogenic stage-specific
gene expression profiles from tissues of yeast artificial chromosome
transgenic mice using chemically induced growth signals.


 2/TI/7
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

  A microtubule associated protein (hNUDC) binds to the extracellular
domain of thrombopoietin receptor (Mpl).


 2/TI/8
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.
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Isolation of endothelial progenitor cells from cord blood and induction of differentiation by ex vivo expansion.

2/TI/9

Identification of the salmon somatolactin receptor, a new member of the cytokine receptor family.

2/TI/10

A case of familial thrombocytosis: possible role of altered thrombopoietin production.

2/TI/11

Selective modification of eukaryotic initiation factor 4F (eIF4F) at the onset of cell differentiation: recruitment of eIF4GII and long-lasting phosphorylation of eIF4E.

2/TI/12

[Synthesis and function analysis of a new thrombopoietin (TPO) mimic peptide]

2/TI/13

Emerging links between initiation of translation and human diseases.

2/TI/14

Crystallization of the functional domain of human thrombopoietin using an antigen-binding fragment derived from neutralizing monoclonal antibody.

2/TI/15

Effect of gravity change on thrombopoiesis in mice.

2/TI/16

Effect of gravity change on the production of thrombopoietic growth factors.

2/TI/17

Implications of mutations in hematopoietic growth factor receptor genes in congenital cytopenias.

2/TI/18

The platelet thrombopoietin receptor number and function are markedly decreased in patients with essential thrombocythaemia.

2/TI/19

A structure-function analysis of serine/threonine phosphorylation of the thrombopoietin receptor, c-Mpl.

2/TI/20

Structure and expression of mGDF, a new member of the transforming growth factor-beta superfamily in the bivalve mollusc Crassostrea gigas.

2/TI/21
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Functional analysis of the C-terminal region of recombinant human thrombopoietin. C-terminal region of thrombopoietin is a "shuttle" peptide to help secretion.

2/TI/22
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Expression of a foreign protein in human megakaryocytes and platelets by retrovirally mediated gene transfer.

2/TI/23
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Adhesion of mature polyploid megakaryocytes to fibronectin is mediated by beta 1 integrins and leads to cell damage.

2/TI/24
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Endomitosis of human megakaryocytes are due to abortive mitosis.

2/TI/25
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Neutralization of biological activity and inhibition of receptor binding by antibodies against human thrombopoietin.

2/TI/26
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Identification of functionally important residues of human thrombopoietin.

2/TI/27
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Peptide, disulfide, and glycosylation mapping of recombinant human thrombopoietin from ser1 to Arg246.

2/TI/28
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Functional analysis of the cytoplasmic domain of the human Mpl receptor for tyrosine-phosphorylation of the signaling molecules, proliferation and differentiation.

2/TI/29
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Identification of an oncogenic form of the thrombopoietin receptor MPL using retrovirus-mediated gene transfer.

2/TI/30
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Dissection of c-Mpl and thrombopoietin function: studies of knockout mice and receptor signal transduction.

2/TI/31
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

Structure and transcription of the genomic locus encoding murine c-Mpl, a receptor for thrombopoietin.

2/TI/32

Human thrombopoietin: gene structure , cDNA sequence, expression, and chromosomal localization.
? t s2/3,ab/17, 26, 27

2/3,AB/17

14177874 PMID: 11458519
Implications of mutations in hematopoietic growth factor receptor genes in congenital cytopenias.
Germeshausen M; Ballmaier M; Welte K
Pediatric Hematology and Oncology, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany.
Annals of the New York Academy of Sciences (United States) Jun 2001, 938 p305-20; discussion 320-1, ISSN 0077-8923--Print Journal Code: 7506858
Publishing Model: Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Mutations in the genes of hematopoietic growth factor receptors as a cause of congenital cytopenia, such as congenital amegakaryocytic thrombocytopenia (CAMT) or severe congenital neutropenia (CN), are discussed. There are striking differences in the relevance of receptor mutations in these diseases. CAMT is a rare disease characterized by severe hypomegakaryocytic thrombocytopenia during the first years of life that develops into pancytopenia in later childhood. In patients with CAMT, we found inherited mutations in c-mpl, the gene coding for the thrombopoietin receptor, in 8 out of 8 cases. The type of mutation seems to correlate with the clinical course seen in the patients. Functional studies demonstrated defective thrombopoietin (TPO) reactivity in hematopoietic progenitor cells and platelets in CAMT patients. CN is a group of hematopoietic disorders characterized by profound, absolute neutropenia due to a maturation arrest of myeloid progenitor cells. About 10% of all patients develop secondary MDS/leukemia. The malignant progression is associated with acquired nonsense mutations within the G-CSF receptor gene that lead to the truncation of the carboxy-terminal cytoplasmic domain of the receptor protein involved in maturation of myeloid progenitor cells. This seems to be one important step in leukemogenesis in CN patients. CAMT is caused by inherited mutations in c-mpl, the gene for the thrombopoietin receptor, which lead to reduced or absent reactivity to TPO. In contrast, mutations in the G-CSF receptor in CN are acquired and are most probably connected with progression of the neutropenia into MDS/leukemia as a result of a loss of differentiation signaling.

2/3,AB/26

12560111 PMID: 9417073
Identification of functionally important residues of human thrombopoietin.
Park H; Park S S; Jin E H; Song J S; Ryu S E; Yu M H; Hong H J
Protein Engineering Research Group, Korea Research Institute of Bioscience and Biotechnology, KIST, P. O. Box 115, Yusong, Taejon 305-600, Korea.
Journal of biological chemistry (UNITED STATES) Jan 2 1998, 273 (1) p256-61, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Thrombopoietin (TPO) is a megakaryocyte growth and differentiation factor. It consists of a characteristic two domain structure. The amino-terminal domain of TPO has a sequence homology with erythropoietin and is required for the binding and activation of its receptor c-Mpl. To determine the functionally important regions interacting with its receptor, a series of site-directed mutants of TPO were constructed based on a three-dimensional model of the amino-terminal domain. Two strategies of mutagenesis were employed: 1) nonnative N-linked glycosylation scan of 12 residues predicted to be on the surface, and 2) alanine replacement scan of mostly charged 44 amino acid residues. Each TPO mutein was transiently expressed in COS7 cells, and the specific bioactivity of the TPO protein secreted into the culture medium was measured using a recombinant BaF3 cell line expressing human c-Mpl. Four alanine substitutions at Arg10, Pro42, Glu50, and Lys138 nearly or completely abolished the activity, whereas the mutation at Arg14 slightly decreased the activity, suggesting that these

residues are functionally important in interacting with its receptor. These residues mapped to helix A, loop AB, and helix D. Sequence comparison between human TPO and other mammalian TPO showed that the identified residues are completely conserved among the species. However, unlike the recent report on the mutational **analysis** of TPO, alanine substitutions at Lys52, Lys59, Arg136, and Arg140 did not affect the TPO activity significantly in our system. The identified receptor binding regions of TPO are analogous to those of human growth hormone and erythropoietin. Based on the similarity of these three cytokines, we propose that Lys138 of helix D and Pro42 and Glu50 of loop AB may constitute one binding region, whereas Arg10 and Lys14 of helix A may constitute the other binding region to dimerize the receptors.

12011948 PMID: 8942648
Peptide, disulfide, and glycosylation mapping of recombinant human thrombopoietin from ser1 to Arg246.
Hoffman R C; Andersen H; Walker K; Krakover J D; Patel S; Stamm M R; Osborn S G
Department of Biological Structure, ZymoGenetics, Inc., Seattle, Washington 98102, USA.
Biochemistry (UNITED STATES) Nov 26 1996, 35 (47) p14849-61, ISSN 0006-2960--Print Journal Code: 0370623
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Thrombopoietin (TPO) is a hematopoietic factor involved in the regulation of megakaryocytopoiesis. Full length recombinant human TPO (332 residues) has been expressed in BHK cells and purified to homogeneity using conventional means. Peptide, disulfide, and glycosylation mapping of human TPO from residues 1 to 246 has been carried out using liquid chromatography-electrospray mass spectrometry (LC-ESMS). A modification of the ramped orifice method of Carr and co-workers [Carr et al. (1993) Protein Sci. 2, 183-196] is employed, providing additional information for assignment of the LC-ESMS chromatograms. With the modification, b- and y-series peptide ions are produced via front-end CID which confirms the mass-based assignments. The results of our **analysis** of TPO indicate that the amino acid sequence of TPO 1-246 is as expected from the transfected cDNA with complete cleavage of the signal peptide. Two unique disulfides are formed between the four cysteines in the cytokine domain of TPO: Cys7-Cys151 and Cys29-Cys85. The glycosylation map indicates the position, occupancy, and structures of the N- and O-glycans in TPO 1-246. In addition, site specific **structural** characterization of the PNGase F-liberated N-glycans has been performed following purification by high-pH anionic exchange chromatography with pulsed amperometric detection (HPAEC-PAD); the results corroborate the LC-ESMS data. The N-glycans are of the complex type with the core-fucosylated disialylated biantennary and trisialylated triantennary structures predominating. The O-glycans are of the mucin type with the monosialylated and disialylated Gal(Gal/NAc-S/T structures predominating. Furthermore, we propose that the C-terminal domain of TPO be further divided into two domains on the basis of sequence homology among the cloned sequences and glycosylation/**structural** features: an N-glycan domain (154-246) and an O-glycan domain (247-332).